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Studies on the Relationship between the Qualities of Substitute Stomachs and the Occurrence of the Dumping Syndrome after Total Gastrectomy

by

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Introduction

The dumping syndrome, troublesome symptoms occurring early after meals in the patients with gastrectomy or gastroenterostomy, limits food intake and results in nutritional deficiency. Because total gastrectomy produces inevitable nutritional deficiencies by inadequate uptake and assimilation of food, the prevention of the dumping syndrome is an important problem in postoperative malnutrition. The various methods of reconstruction following total gastrectomy have been invented to prevent the so-called agastric syndrome²⁷⁾⁴⁴⁾⁵⁶⁾⁵⁹⁾. Regarding the prevention or treatment of the dumping syndrome, attention is focused on the prevention of the rapid intake of meals into the upper jejunum. However, little work has been done to investigate this point from the standpoint of the qualities of substitute stomach.

Based on KIMURA's suggestion, ISHIGAMI²³⁾ invented a new type of operation, total gastrectomy with preservation of the hepatic and posterior celiac vagi. Our observations on this type of total gastrectomy revealed that the postoperative complications, such as diarrhea, anorexia and weightloss occurred less frequently, and fat absorption, carbohydrate metabolism and gallbladder function were markedly improved, as compared with those in the conventional total gastrectomy with truncal vagotomy¹⁴⁾¹⁵⁾²⁴⁾²⁶⁾.

However, we were impressed by the more frequent occurrence of the dumping syndrome after this type of gastrectomy. WAKABAYASHI⁶⁸⁾, in our laboratory, observed that the division of the posterior celiac vagi suppressed vasomotor changes and also the disappearance of 5-hydroxytryptamine (serotonin) fluorescence in the jejunal mucosa in response to intrajejunal hypertonic glucose. These observations suggest that vagal innervation in a substitute stomach is closely related to the occurrence of the dumping syndrome.

On the other hand, recent studies revealed important roles of the humoral agents including serotonin and systemic and portal hemodynamics in the dumping syndrome¹⁷⁾⁴⁹⁾⁵¹⁾⁵²⁾⁵⁷⁾⁶⁰⁾⁶⁴⁾. For the prevention of this syndrome, reasonable countermeasures should be

Key words : Substitute stomach, Dumping syndrome, Total gastrectomy, Vagotomy, Serotonin

considered on the basis of these pathogeneses.

The present study was designed to determine the relationship among the occurrence of the dumping syndrome and such points of substitute stomachs, as intestinal varieties, vagal innervation and types of reconstruction, by measuring changes in blood serotonin levels and systemic hemodynamics as indicators of this syndrome.

Materials and Methods

A. Animal experimentation

1. Animals and anesthesia

Healthy, fasted adult mongrel dogs weighing 6 to 16 kilograms were anesthetized with an intramuscular ketamine injection in a dose of 50 milligrams per kilogram of body weight.

2. Experimental process

i) Vagotomy (Fig. 1)

Through a midline abdominal incision the hepatic or the posterior celiac vagus was selectively divided. The experiments were performed about two weeks after the vagotomy.

ii) Experimental modes of pedunculated transposition of the intestinal segment as substitute stomach (Fig. 2)

Because the dogs usually suffer from fatal malnutrition after total gastrectomy, the pedunculated upper jejunal or upper colonic segment approximately 30 centimeter in length was used as a substitute stomach and its distal end was anastomosed to the side of the duodenum. Regarding the pedunculated transposition of the jejunal segment as substitute stomach, figure 6-shaped loop or double tract was made.

iii) Dumping test (Fig. 3)

The dumping stimulus was performed by the administration of 10 milliliter of 50 per cent glucose solution per kilogram of body weight within 3 minutes into the distal jejunum through the Nélaton catheter, which was introduced into the duodenum about 10 centimeter distal to the pyloric ring. The duodenum was ligated just distal to the pyloric ring.

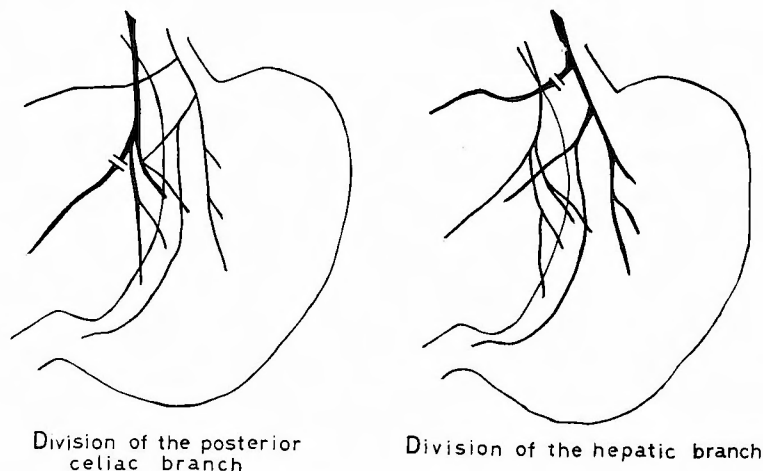


Fig. 1 Vagotomy in dogs

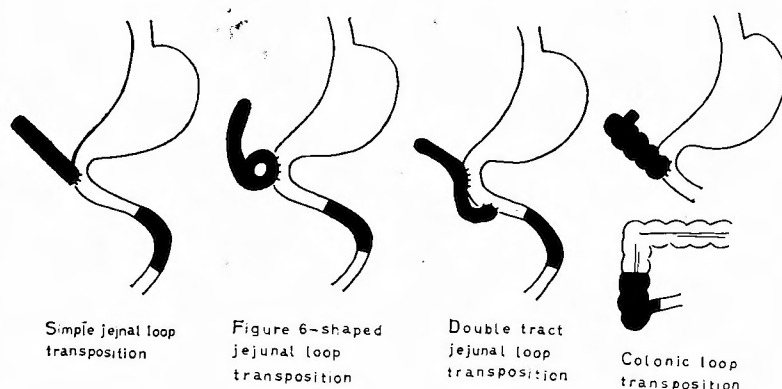


Fig. 2 Intestinal transposition in dogs

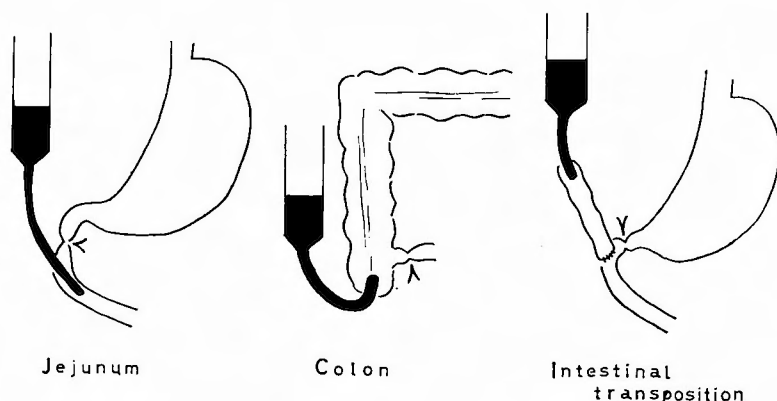


Fig. 3 The dumping test following intrainstestinal glucose administration in dogs

As the dumping stimulus in the upper colon, the terminal ileum was ligated and hypertonic glucose solution was instilled through the coecum into the ascending colon. In the transposed intestinal segment, hypertonic glucose solution was instilled through the Nélaton catheter which was introduced into the proximal end of the transposed intestinal segment.

iv) Blood sampling (Fig. 4)

For the sampling of portal blood, the splenic vein was cannulated with a polyethylene catheter which was inserted into the portal vein, the tip lying immediately proximal to the bifurcation of the portal vein. A splenectomy was then performed.

In the transposed intestinal segment, blood circulation of the stomach was intercepted, in imitation of total gastrectomy. Another polyethylene catheter was introduced into the femoral vein for sampling of systemic venous blood.

Samples of hepatic venous blood were collected by the following method. A laparotomy with a right thoracotomy was performed and the inferior vena cava was exposed. A polyethylene catheter for sampling hepatic venous blood was inserted through the right external jugular vein into the inferior vena cava, the tip lying immediately proximal to the diaphragm. A strong silk thread was applied around the inferior vena cava just cranial to

the origin of the renal vein and another strong silk thread was applied around the inferior vena cava cranial to the distal end of the polyethylene catheter. The inferior vena caval circulation was intercepted by lifting both silk threads applied around the inferior vena cava. After the remaining hepatic venous blood mixed with the inferior vena caval blood was aspirated through the catheter, hepatic venous blood was collected.

3. Methods of measurement

i) Measurement of femoral artery pressure, pulse pressure and circulating plasma volume

Femoral artery pressure and pulse pressure were measured with an electro-sphygmomanometer (Nippon Kodon MP-4 type) through the polyethylene catheter introduced in the left femoral artery.

Circulating plasma volume was calculated by the GIBSON & EVANS method and the density of Evans' blue dye in blood plasma was measured with a Hitachi ultravioletvisible spectrophotometer.

ii) Measurement of blood serotonin (Table 1)

Measurement of blood serotonin was made by the method described by UDENFRIEND, WEISSBACH and BRODIE using the Aminco-Bowman spectrophotofluorimeter with activation at 295 millimicra and emission at 550 millimicra. The serotonin values of unknown samples were obtained directly from a calibration curve.

iii) Fluorohistochemical study (Table 2)

A small piece of the upper jejunum or the upper colon was removed before and 30 minutes after administration of hypertonic glucose solution, and serotonin release from the argentaffin cell mass in the intestinal wall was observed fluorohistochemically according to the FALCK-FUJIWARA method.

B. Clinical materials (Fig. 5)

1. Total gastrectomy with preservation of the hepatic and posterior celiac vagi

The whole stomach was mobilized except for the upper portion of the lesser curvature and the cardiac end of the greater curvature. The visceral peritoneum anterior to the abdominal esophagus was incised trasversely just above the cardia, then the anterior vagal trunk was identified anterior to the esophagus.

The hepatic vagal branches could easily be seen passing to the right, then the hepatic branches were dissected distally from their origins in the anterior vagal trunk, after

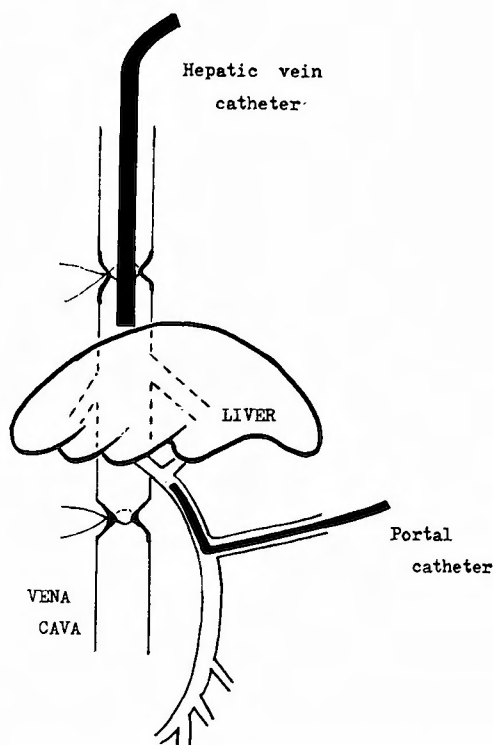


Fig. 4 Sampling of portal and hepatic vein blood

Table 1. Methods of Biochemical Analysis of Serotonin

	Unknown	Blank	Standards
Blood	1 ml.		
Water	4 ml.	5 ml.	4 ml.
Standards			1 ml.
Zinc sulfate	1 ml.	1 ml.	1 ml.
NaOH	0.5 ml.	0.5 ml.	0.5 ml.
Mix well and centrifuge.			
↓			
Transfer an aliquot of each supernatant fluid and adjust PH to 10.0 with anhydrous sodium carbonate.			
↓			
Add 5ml. of borate buffer and dilute to a volume of 15 ml. with distilled water. Add 5 g. NaCl and 15 ml. of n-butanol. Shake and centrifuge.			
↓			
Decant the supernatant fluid and centrifuge.			
↓			
Remove the bottom layer and wash the butanol phase with a borate buffer.			
↓			
Transfer 10 ml. of butanol phase to a glass-stoppered tube containing 20 ml. of heptane and 1.5 ml of 0.1 N HCl. Shake and centrifuge.			
↓			
Remove 1 ml. of the dilute HCl solution and add 0.3 ml. of 12 N HCl.			
↓			
Measure its fluorescence on the Aminco spectrofluorimeter.			

Table 2. Histochemistry of Serotonin (FALCK-FUJIWARA method)

pieces of the tissues to be studied were immediately excised
↓
frozen in isopentan cooled by acetone + dry ice.
↓
dried in vacuum at -35°C for 2 to 7 days.
↓
treated with formaldehyde gas at +80°C for 1 hour in a closed glass vessel containing paraformaldehyde
↓
infiltrated in vacuum with paraffin at +60°C for 10 to 20 min.
↓
fresh-frozen sections were cut at will
↓
enclosed in entellan + xylene
↓
examined under a fluorescence microscope

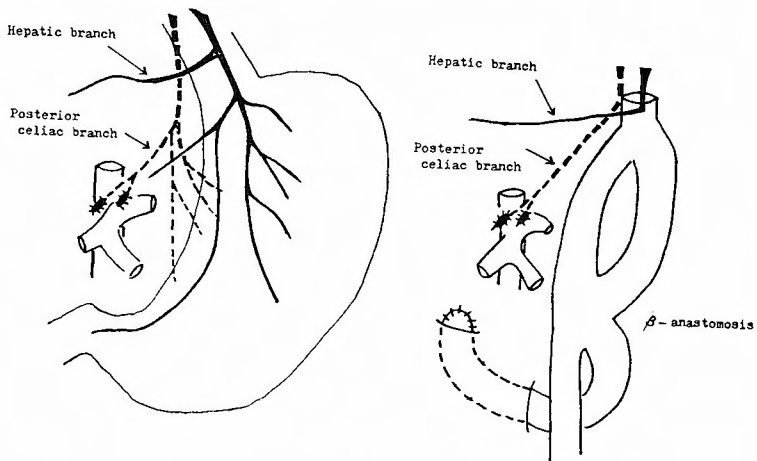


Fig. 5 Total gastrectomy with preservation of the hepatic and posterior celiac branches (KIMURA & ISHIGAMI)

dividing the anterior gastric and anterior celiac branches at their constant original portions just beneath the peritoneum adjacent to the cardia and lesser curvature. With downward traction on the stomach, the posterior trunk or its celiac branch was palpated and identified as a taut cord by a finger directed alongside the right posterior surface of either the abdominal esophagus and cardia, and the whole course of the celiac branch was dissected down to the trunk of the left gastric artery or to the celiac plexus. The left gastric vessels were divided near the origin of the artery from the celiac artery. After visualization of the whole course of the celiac branches situated craniodorsal to these vessels, the posterior gastric branches were divided just near the origin from the posterior trunk. In this manner, the stomach was completely dissected preserving the hepatic and posterior celiac branches of the vagi. After total gastrectomy usually esophagojejunostomy plus jejunojejunostomy of β type (NAKAYAMA) was performed.

2. Analysis of dumping symptoms

(Table 3)

The patients were inquired about subjective symptoms of the dumping syndrome as proposed by the committee in the fourth congress of Japanese Gastroenterological Surgery, one to twelve months after total gastrectomy. The patients with absolute non-curative resection, recurrence of cancer and complications were excluded.

3. Dumping test

After morning fast, the patients were

Table 3. Early dumping syndrome

General Symptoms	A	1	Cold sweating
		2	Palpitation
		3	Dizziness
		4	Feeling of numbness
	B	5	Flushing of the face
		6	Pallor of the face
		7	Flushing
		8	Fatigability
		9	Sleepiness
		10	Head heavy sensation
		11	Precordial oppression
Intestinal Symptoms	C	13	Borborygmus
		14	Abdominal pain
		15	Diarrhea
	D	16	Nausea
		17	Vomiting
		18	Abdominal fullness
		19	Abdominal discomfort

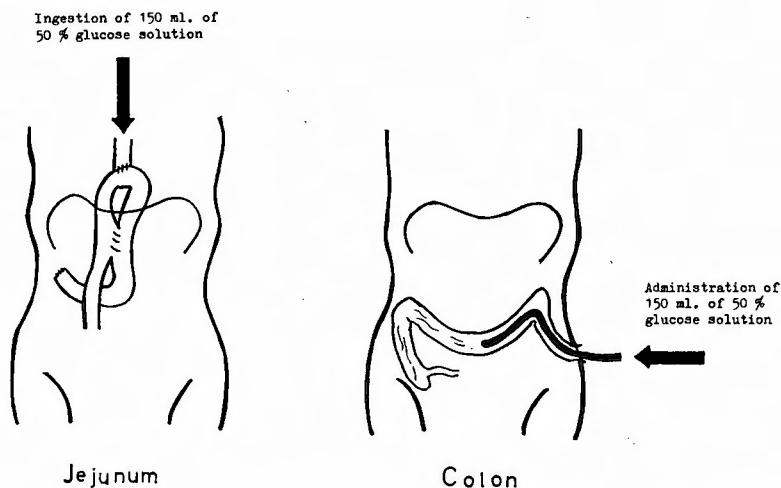


Fig. 6 Dumping test in human being

given an oral hyperosmolar stimulus of 150 milliliter of 50 per cent glucose solution within a 3-minute-period, one to two months after total gastrectomy. The patients with artificial anus in the sigmoid colon were given hyperosmolar stimulus of 150 milliliter of 50 per cent glucose solution, through the Nélaton catheter which was inserted into the artificial anus, the tip lying toward the transverse colon (Fig. 6).

The incidence of subjective symptoms was observed and blood pressure, pulse rate, circulating plasma volume and skin temperature in fingertips were measured before and 10, 20 and 30 minutes after glucose ingestion. Circulating plasma volume was calculated by GIBSON & EVANS method.

Blood serotonin was measured according to the method of UDENFRIEND et al., before and 10 and 30 minutes after glucose ingestion.

Results

A. Animal experimentation

I. Intestines and dumping responses

1. Dumping responses in the jejunum and colon
- i) Systemic hemodynamics (Fig. 7, 8)

In the dumping test following intrajejunal and intracolonic administration of hypertonic glucose solution in dogs, the maximal changes of femoral artery pressure and pulse pressure occurred within 10 to 20 minutes after glucose administration (Fig. 7).

The average maximal per cent decreases in femoral artery pressure, pulse pressure and circulating plasma volume were 23.1 ± 3.82 per cent, 23.0 ± 5.96 per cent and 15.0 ± 3.78 per cent, respectively, in the group of the jejunum, while they were 2.3 ± 0.97 per cent, 5.21 ± 1.68 per cent and 1.8 ± 1.88 per cent, respectively, in the group of the colon. These differences were statistically significant ($p < 0.01$, $p < 0.05$ and $p < 0.05$) (Fig. 8).

- ii) Portal and systemic vein serotonin (Fig. 9)

The average per cent increases in portal serotonin levels in the group of the jejunum

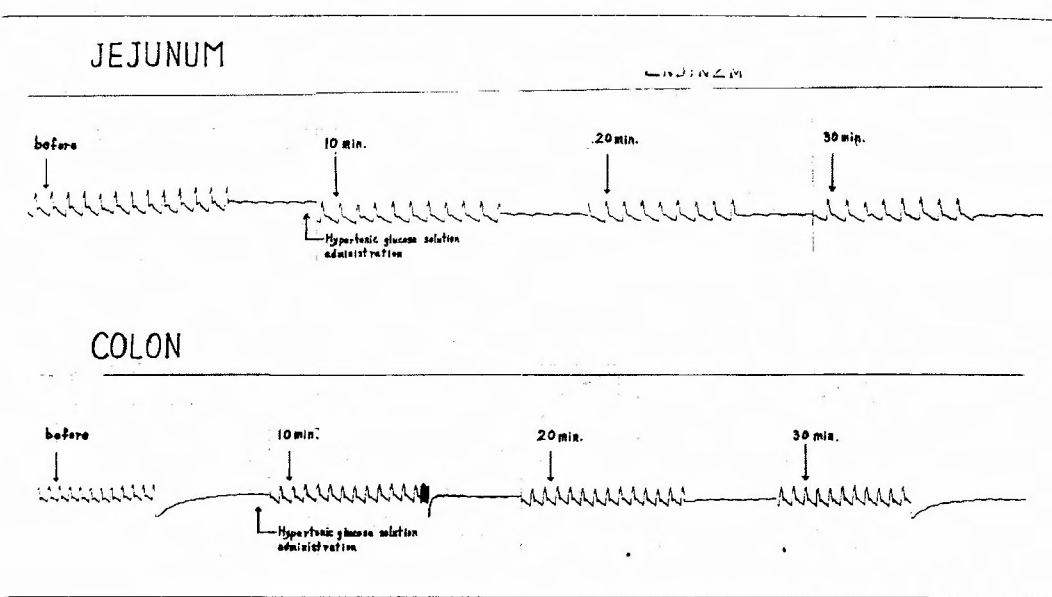


Fig. 7 The changes in femoral artery pressure and pulse pressure in dogs

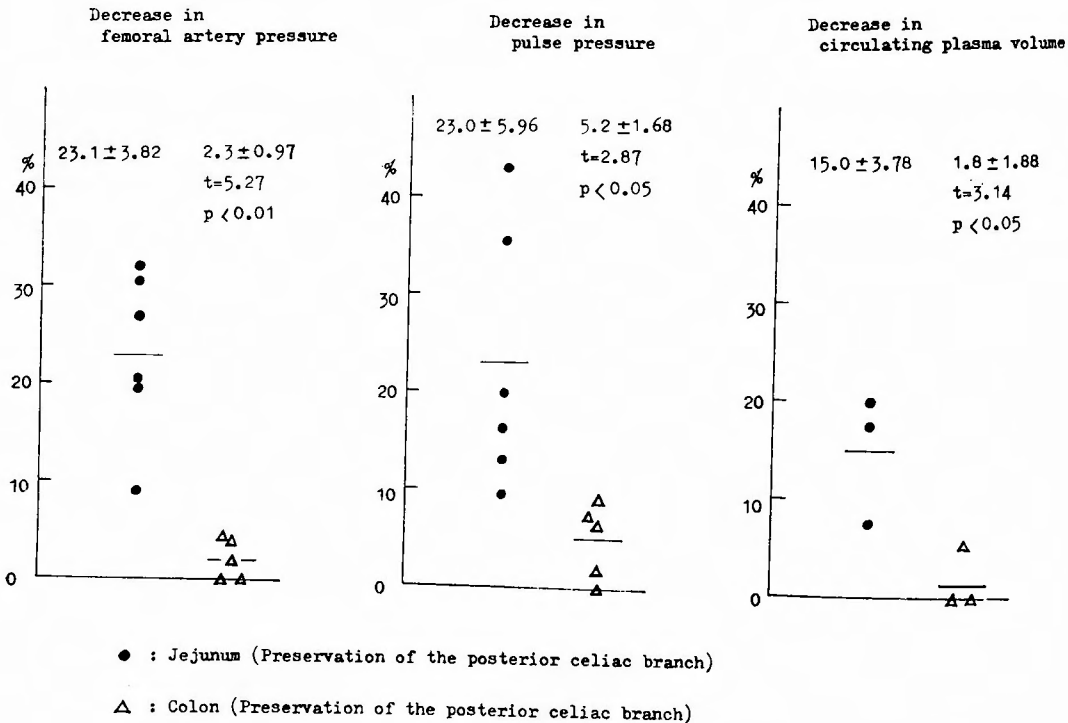


Fig. 8 Changes in systemic hemodynamics in the dumping test following glucose administration in dogs

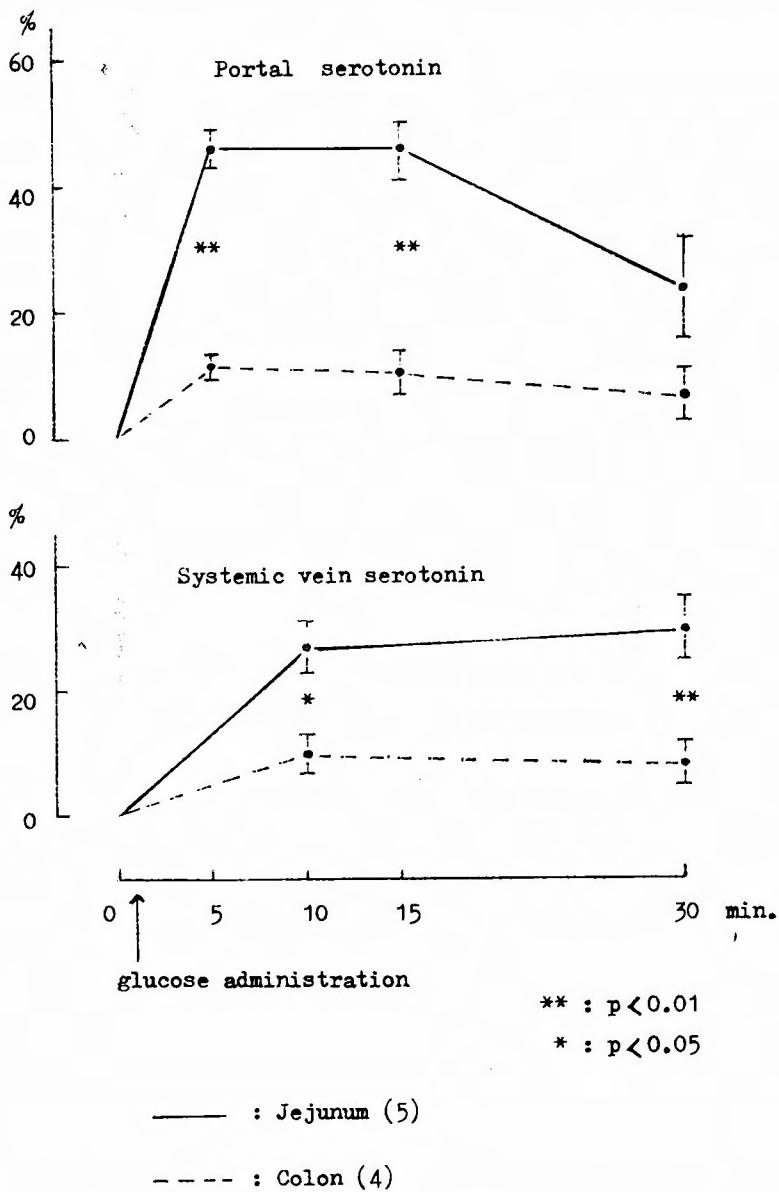


Fig. 9 Increase in blood serotonin levels after glucose administration in dogs

were 45.8 ± 2.81 per cent and 45.6 ± 4.51 per cent, respectively, and 11.6 ± 2.05 per cent and 10.5 ± 3.37 per cent, respectively, in the group of the colon, 5 and 15 minutes after glucose administration (upper column in Fig. 9).

The average per cent increases in systemic vein serotonin levels in the group of the jejunum were 25.9 ± 3.53 per cent and 29.6 ± 4.93 per cent, respectively, while they were 9.9 ± 3.37 per cent and 8.6 ± 3.53 per cent, respectively, in the group of the colon, 10 and 30 minutes after glucose administration (lower column in Fig. 9). There was a statistically significant difference between both groups ($P < 0.01$).

no.	Duodenum	Jejunum	Colon
205	+++	+++	++
215	+++	+++	++
219	+++	+++	++

Fig. 10 Distribution of serotonin in the intestinal tract in dogs

Intraluminal pressures of the upper jejunum and upper colon were 9 to 12 cm. H₂O, and increased to 15 to 20 cm. H₂O during the period of the dumping stimulus, and then decreased to 11 to 14 cm. H₂O. There was no significant difference between both groups.

iii) Fluorohistochemical study (Fig. 10, 11).

Fluorohistochemically, the serotonin content in the upper colon was about half of that in the upper jejunum and its decrease following glucose administration was slight as compared with the upper jejunum.

2. Dumping responses in the transposed intestinal segment

i) Systemic hemodynamics (left column in Fig. 12)

The rate of decrease in pulse pressure amounted to 20.2 ± 1.75 per cent in the group of the transposed jejunal segment, while it amounted to 10.6 ± 1.58 per cent in the group of the transposed colonic segment with significant difference ($P < 0.01$). However, there was no significant difference in femoral artery pressure.

ii) Portal and systemic vein serotonin (right column in Fig. 12)

The average per cent increases in portal serotonin levels in the group of the transposed jejunal segment were 48.1 ± 6.36 per cent and 47.4 ± 2.45 per cent, respectively, 5 and 15 minutes after glucose administration, being insignificantly higher than the average per cent increases of 43.8 ± 4.39 per cent and 39.8 ± 2.39 per cent, respectively, in the group of the transposed colonic segment.

Regarding systemic vein serotonin, there was no significant difference between both groups.

II. Vagal innervation and dumping responses

1. Effects of posterior celiac vagotomy on the dumping responses in the jejunum and colon

Colon			
no.	Before		After
205	++	→	+
212	++	→	+

Jejunum			
no.	Before		After
129	+++	→	+
130	+++	→	++
211	+++	→	+

Fig. 11 The change of seotonin after glucose administration in dogs

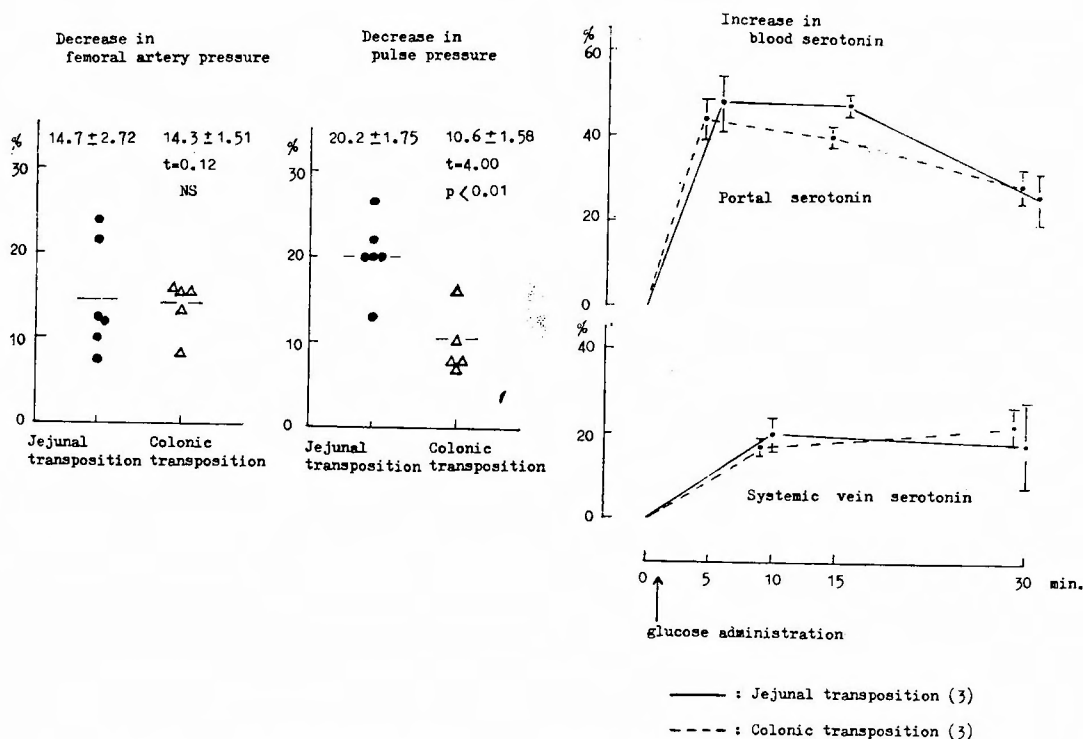


Fig. 12 Changes in systemic hemodynamics and blood serotonin levels after glucose administration in dogs

i) Systemic hemodynamics (Fig. 13, 14)

During the dumping stimulus to the jejunum, the maximal average decreases in femoral artery pressure and pulse pressure amounted to 23.1 ± 3.82 per cent and 23.0 ± 5.96 per cent, respectively, in the group of preservation of the posterior celiac vagus, while they were 6.3 ± 1.73 per cent and 8.4 ± 2.99 per cent, respectively, in the group of posterior celiac vagotomy.

There were significant differences in femoral artery pressure and pulse pressure between both groups ($P < 0.01$ and $P < 0.05$) (Fig. 13).

Regarding the responses of the colon to the dumping stimulus, the changes in femoral artery pressure were slight. Moreover, there were no significant differences between the groups with and without posterior celiac vagotomy (left column in Fig. 14).

ii) Portal and systemic vein serotonin

Portal serotonin levels following the dumping stimulus to the jejunum showed an initial rapid increase followed by a gradual decrease in the preservation group of the posterior celiac vagus, while its increase was slow in the group of division. Namely, the average per cent increases in portal serotonin levels were 45.8 ± 2.31 per cent in the preservation group, and 23.1 ± 2.16 per cent in the division group, 5 minutes after glucose administration. There was a significant difference between both groups ($P < 0.01$) (upper column in Fig. 15). However, the average per cent increases in systemic vein serotonin levels in the preservation group were insignificantly higher than that of the division group (lower

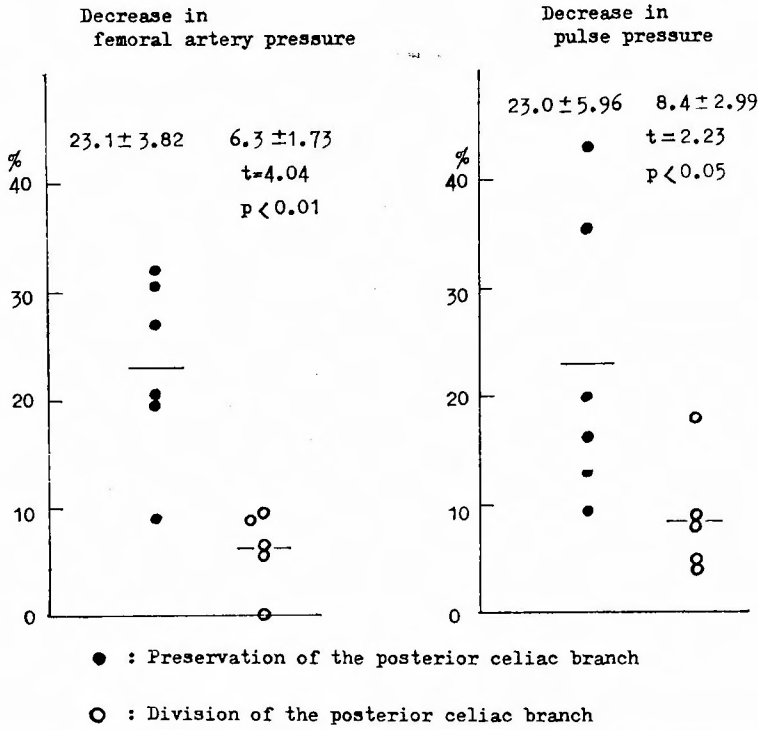


Fig. 13 Decrease in femoral artery pressure and pulse pressure following intrajejunal glucose administration in dogs

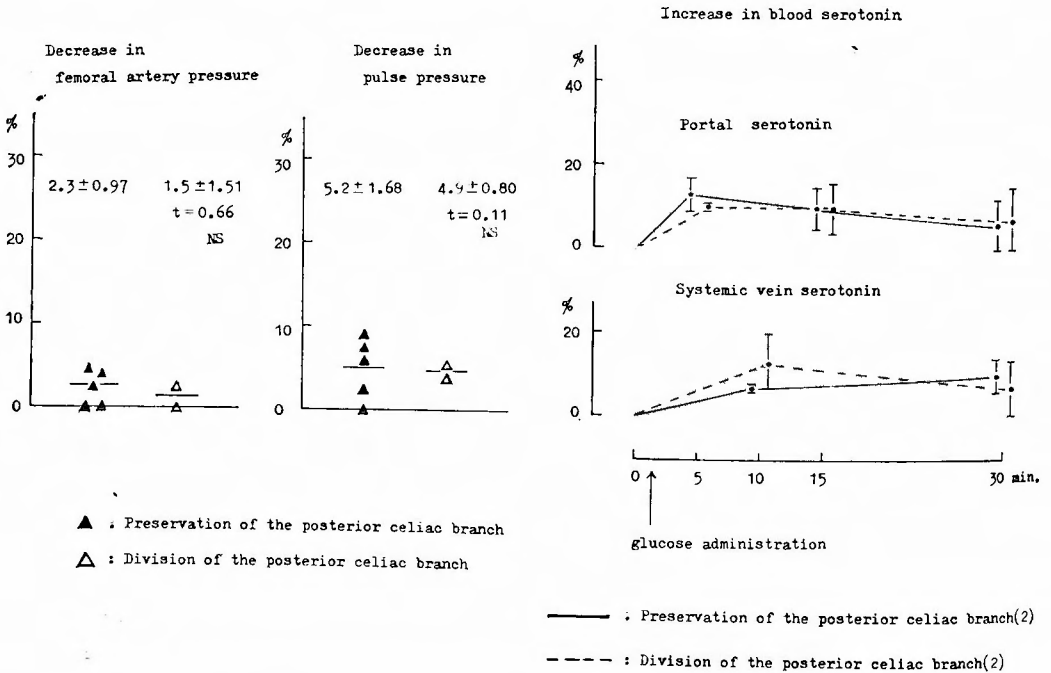


Fig. 14 Changes in systemic hemodynamics and blood serotonin levels following intracolonic glucose administration in dogs

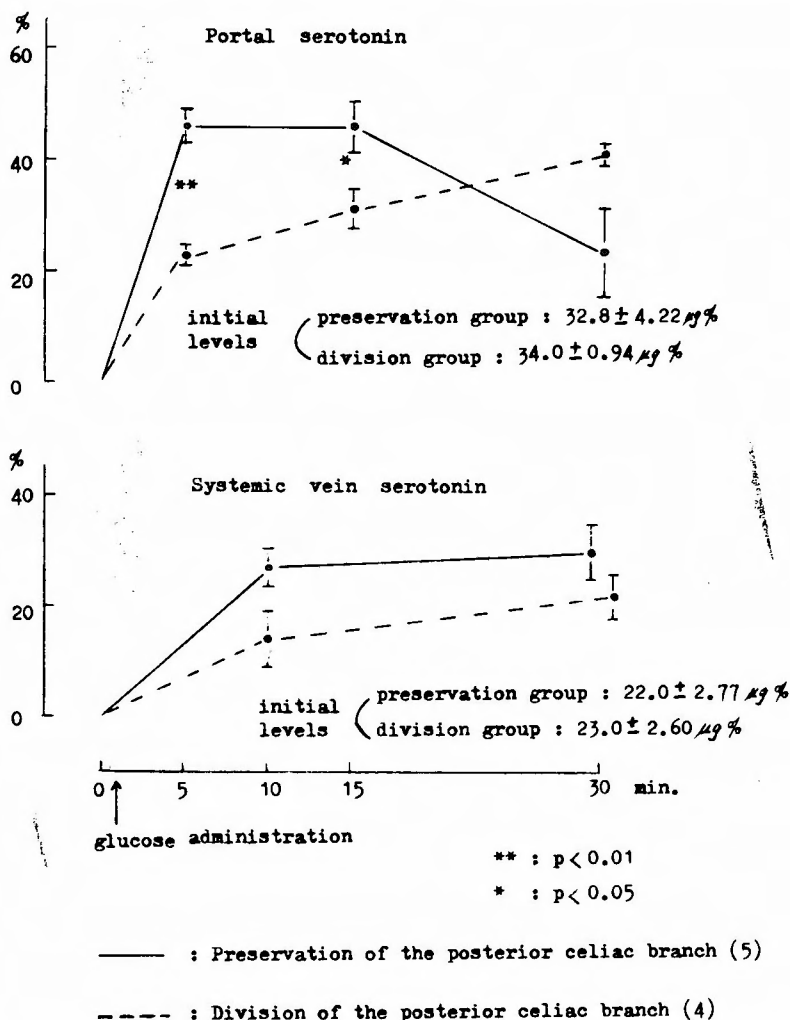


Fig. 15 Increase in blood serotonin levels following intrajejunal glucose administration in dogs (column in Fig. 15).

The increases in portal and systemic vein serotonin levels following the dumping stimulus to the colon were slight and scarcely affected by posterior celiac vagotomy (right column in Fig. 14).

2. Effects of posterior celiac vagotomy on the dumping responses in the transposed intestinal segment

i) Systemic hemodynamics (Fig. 16, 17)

During the dumping stimulus to the transposed jejunal segment, pulse pressure showed 20.2 ± 1.75 per cent decrease in the preservation group of the posterior celiac vagus and 7.7 ± 2.15 per cent decrease in the group with posterior celiac vagotomy. This difference was statistically significant ($P < 0.01$). However, there was no significant difference in femoral artery pressure between both groups (Fig. 16).

In the transposed colonic segment, the rate of decrease in circulating plasma volume

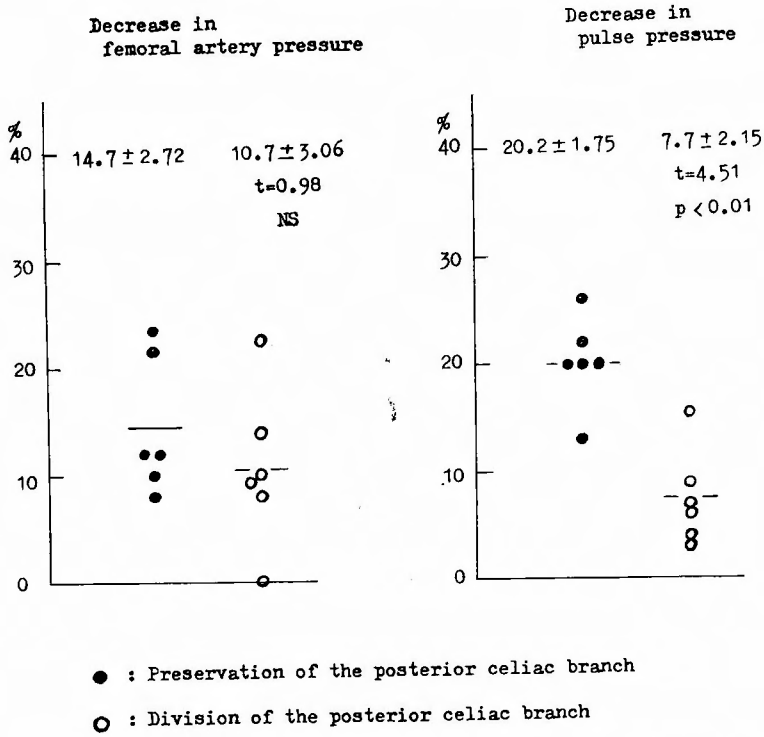


Fig. 16 Changes in femoral artery pressure and pulse pressure following glucose administration into transposed jejunum in dogs

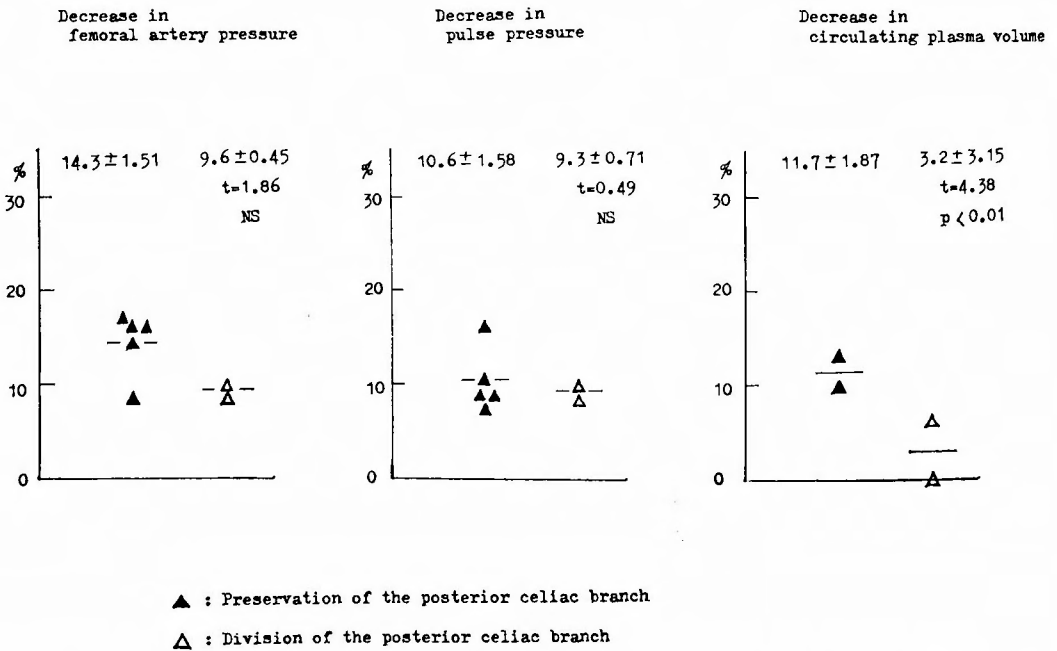


Fig. 17 Changes in systemic hemodynamics following glucose administration into transposed colon in dogs

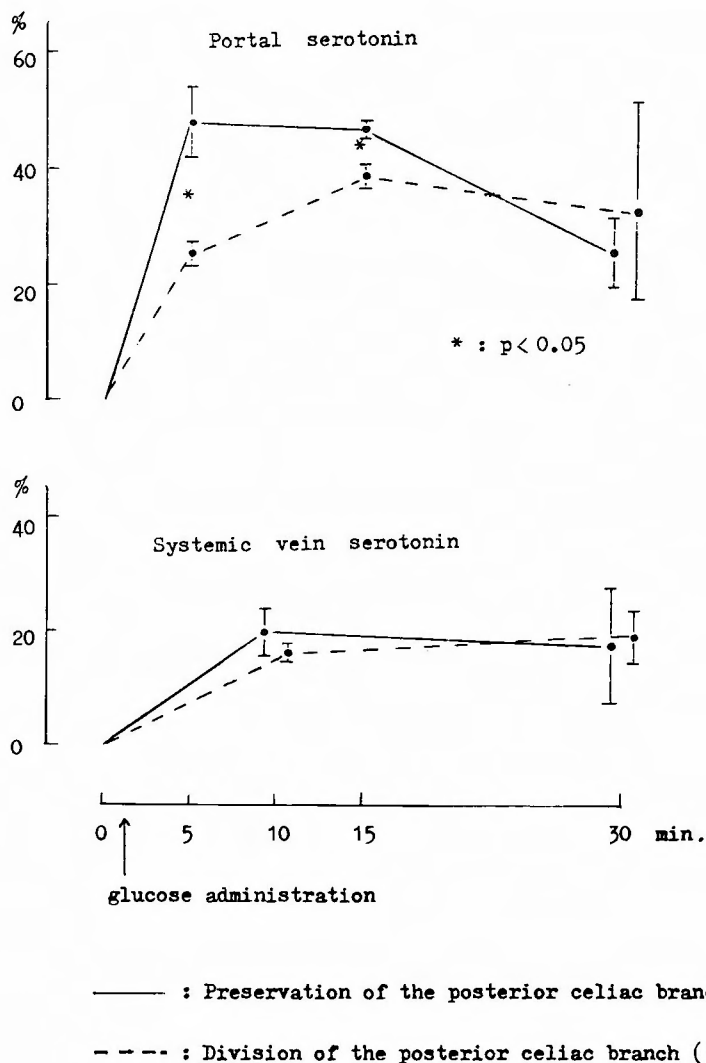


Fig. 18 Increase in blood serotonin levels following glucose administration into transposed jejunum in dogs

was 11.7 ± 1.87 per cent in the preservation group and 3.2 ± 3.15 per cent in the division group. This difference was statistically significant ($P < 0.01$). However, there were no significant differences in femoral artery pressure and pulse pressure between both groups (Fig. 17).

ii) Portal and systemic vein serotonin (Fig. 18)

Portal serotonin levels showed an initial rapid increase in the preservation group, while it showed a tendency to increase gradually in the division group. There was a significant difference in initial increase between both groups (upper column in Fig. 18). In systemic vein serotonin levels, there was no significant difference (lower column in Fig. 18).

3. Effect of hepatic vagotomy on the dumping responses

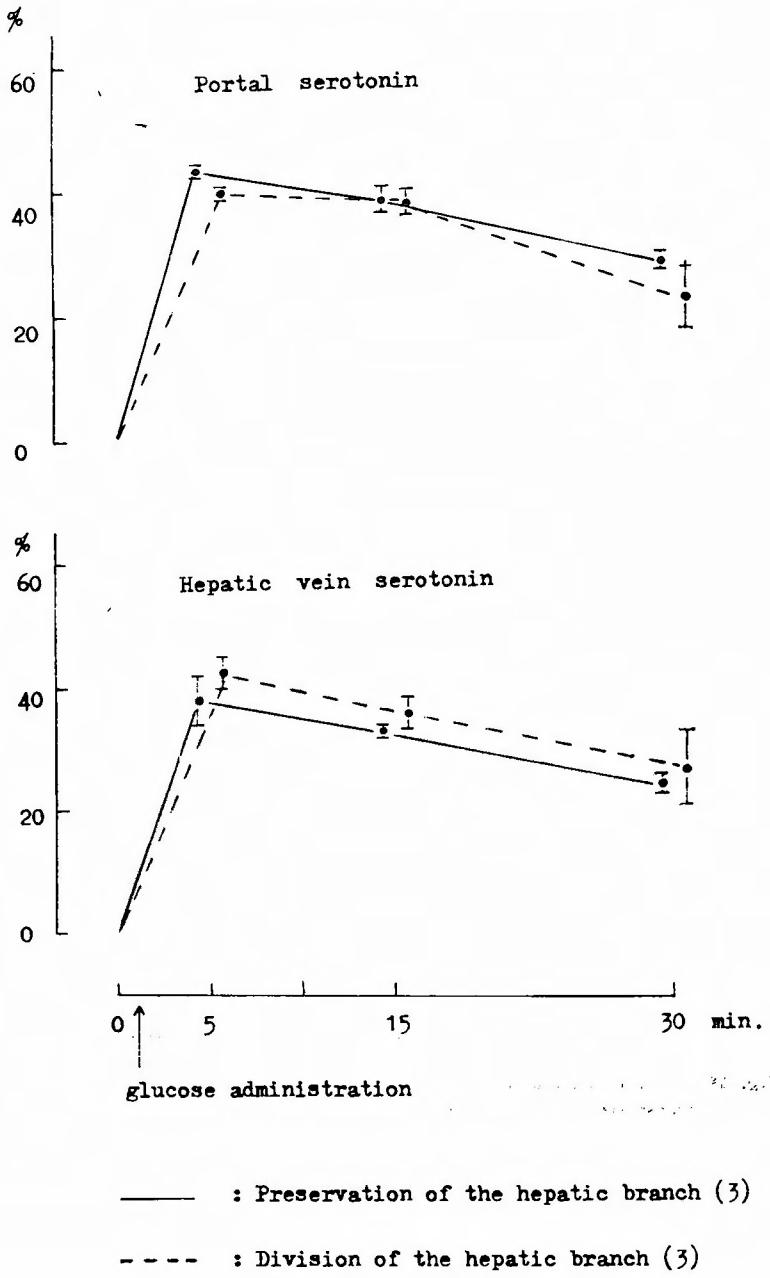


Fig. 19 Increase in blood serotonin levels following intrajejunal glucose administration in dogs

i) Systemic hemodynamics

During the dumping stimulus, the rates of decrease in femoral artery pressure and pulse pressure were almost the same in the groups with and without hepatic vagotomy.

ii) Portal and hepatic vein serotonin (Fig. 19, 20)

The average per cent increases in portal serotonin levels in the group without hepatic

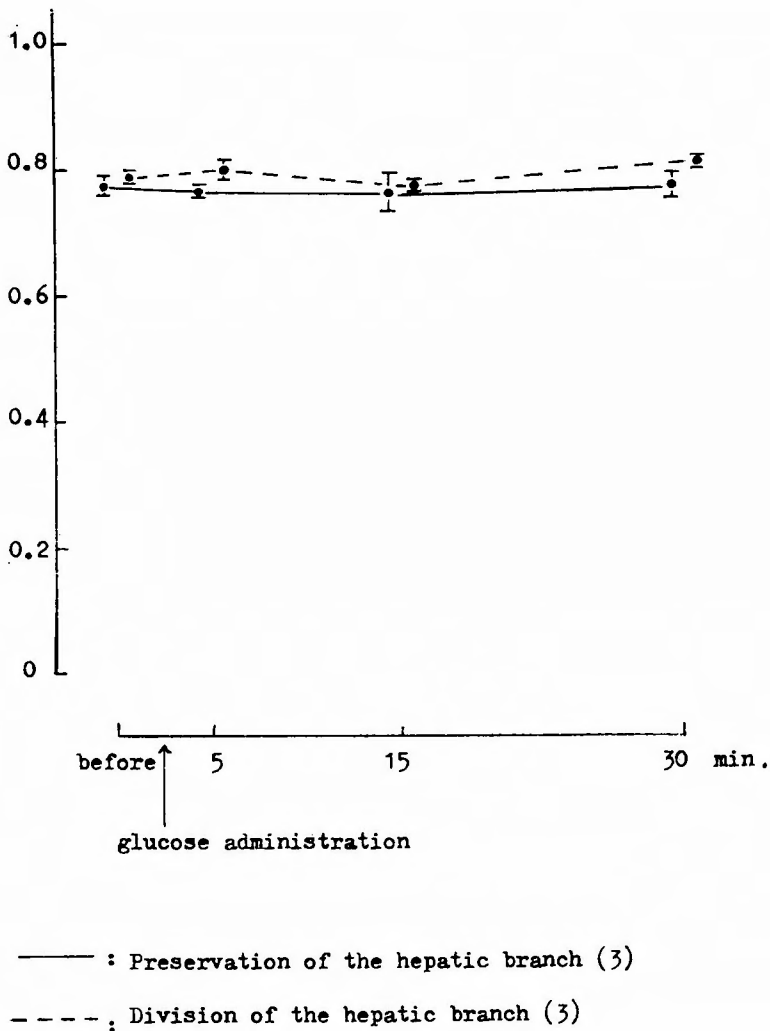


Fig. 20 Clearance of blood serotonin in liver following intrajejunal glucose administration in dogs

vagotomy were 43.6 ± 0.46 per cent, 39.2 ± 2.65 per cent and 28.9 ± 2.41 per cent, respectively, 5, 15 and 30 minutes after glucose administration, while they were 40.3 ± 0.96 per cent, 38.7 ± 2.89 per cent and 23.2 ± 6.90 per cent, respectively, in the group with hepatic vagotomy (upper column in Fig. 19).

The average per cent increases in hepatic vein serotonin levels in the group without hepatic vagotomy were 38.1 ± 4.08 , 33.0 ± 1.61 and 24.5 ± 2.47 per cent, respectively, 5, 15 and 30 minutes after glucose administration, which were slightly lower than the average per cent increases of 42.5 ± 3.82 , 35.8 ± 3.55 and 27.3 ± 8.75 per cent in the group with hepatic vagotomy (lower column in Fig. 19).

Serotonin clearance by the liver is shown in Fig. 20. There was no significant difference between both groups.

III. Type of anastomosis modes and dumping responses

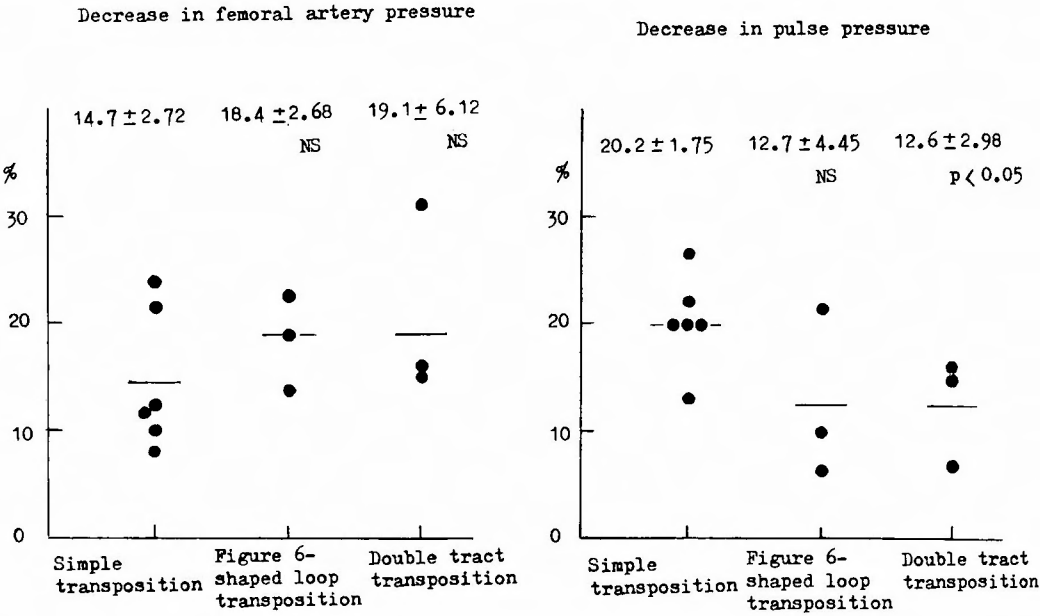


Fig. 21 Changes in femoral artery pressure and pulse pressure following glucose administration into transposed jejunum in dogs

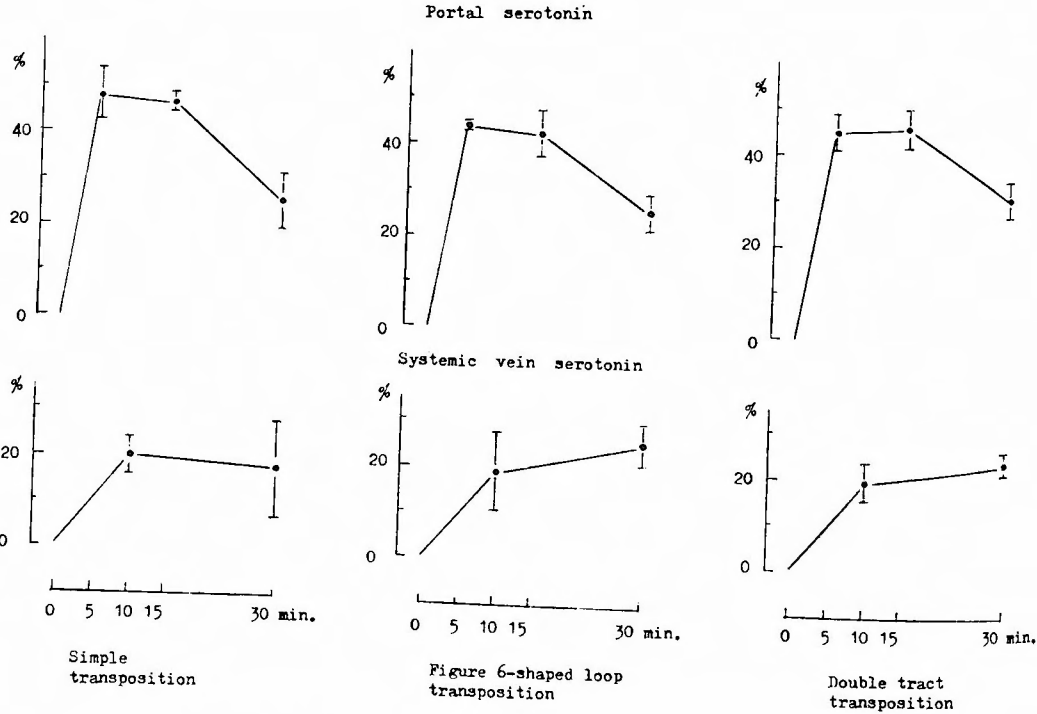


Fig. 22 Increase in blood serotonin levels following glucose administration into transposed jejunum in dogs

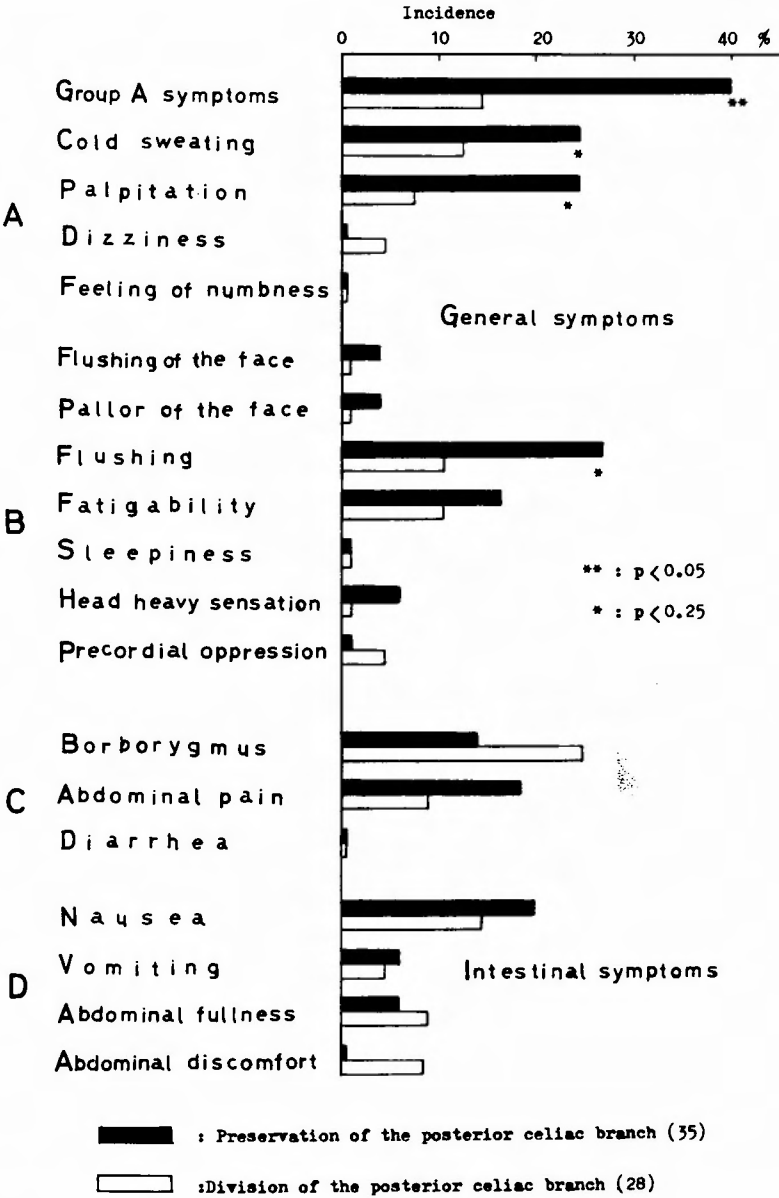


Fig. 23 Subjective complaints in early dumping syndrome after total gastrectomy

i) Systemic hemodynamics (Fig. 21)

The dumping tests were performed in the groups with transposition of the simple jejunal loop, the figure 6-shaped jejunal loop and the double tract jejunal loop. The rate of decrease in femoral artery pressure showed very little difference among these groups. Pulse pressure in the latter two groups showed a tendency to decrease slightly, as compared with the former group, and there was a significant difference between the group with simple and the group with double tract.

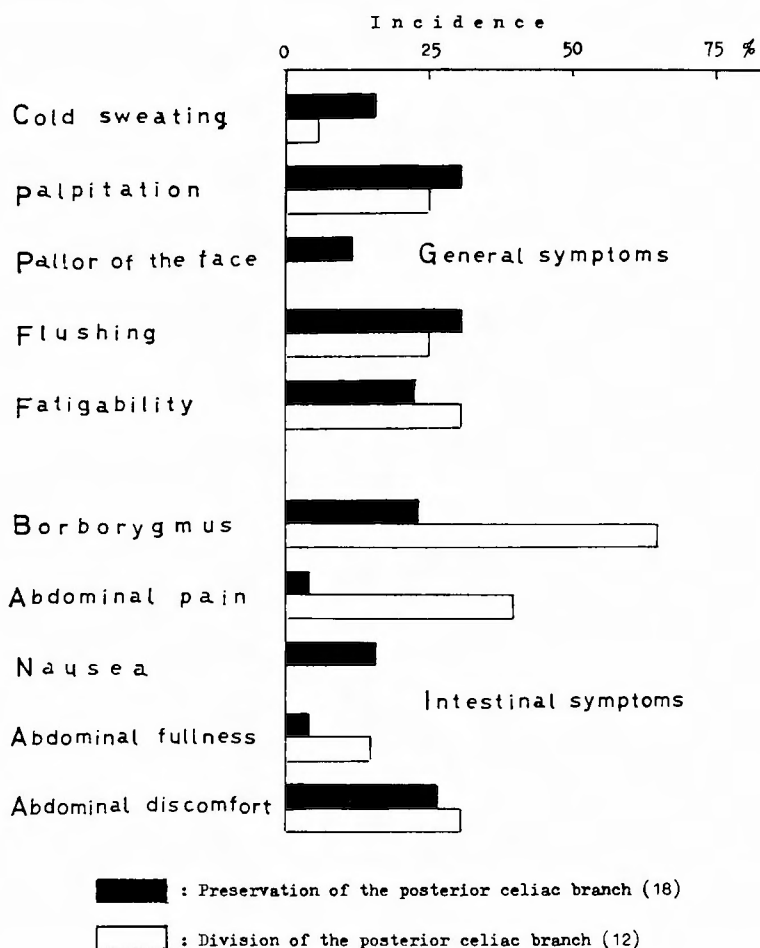


Fig. 24 Subjective complaints in dumping test following glucose ingestion after total gastrectomy

ii) Portal and systemic vein serotonin (Fig. 22)

Portal serotonin levels showed a pattern of initial rapid increase followed by gradual decrease with insignificant difference among these groups.

The average per cent increases in the systemic vein serotonin levels were lower than those of the portal vein, and there were no significant differences among these groups.

B. Clinical observations

I. The dumping syndrome in clinical cases of total gastrectomy with preservation of the hepatic and posterior celiac vagi

1. Subjective symptoms (Fig. 23)

In the cases with total gastrectomy with preservation of the posterior celiac branch, one to twelve months after operation, the incidence of the dumping syndrome was higher than that in the cases of total gastrectomy with truncal vagotomy.

Especially general symptoms such as cold sweating, palpitation, flushing, etc., occurred much more frequently. The incidence of Group A symptoms, the most important dumping

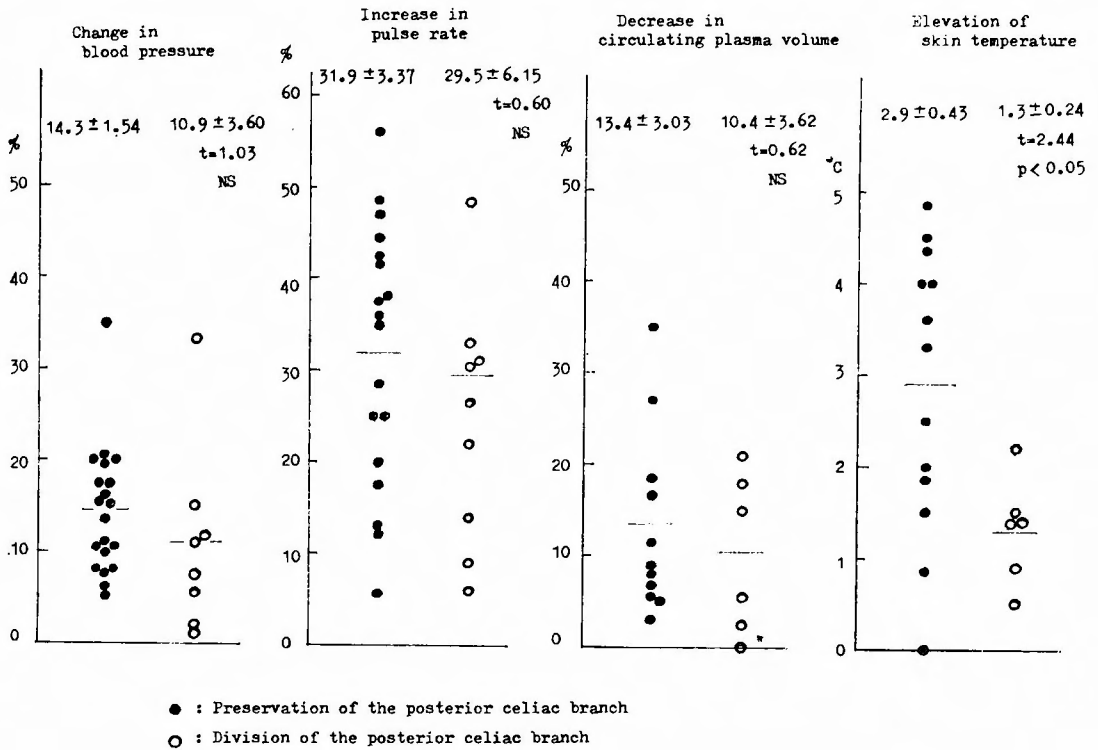


Fig. 25 Changes in systemic hemodynamics following glucose ingestion after total gastrectomy

symptoms consisting of cold sweating, palpitation, dizziness and numbness, was 40 per cent in the cases of preservation, while it was 14 per cent in the cases of total vagotomy. This difference was significant ($P < 0.05$).

2. Dumping test

i) Subjective symptoms (Fig. 24)

In the dumping test following ingestion of 150 milliliter of 50 per cent glucose solution, the incidence of general symptoms such as cold sweating, palpitation, paleface, flushing, etc., was higher in the cases of preservation of the posterior celiac vagus, as compared with in the cases of total vagotomy. On the other hand, intestinal symptoms such as borborygmus, abdominal pain and abdominal fullness tended to occur less frequently in the cases of preservation.

ii) Systemic hemodynamics (Fig. 25)

The cases with preservation of the posterior celiac branch showed 2.9°C. elevation of skin temperature, while the cases with total vagotomy showed 1.3°C. elevation. This difference was statistically significant ($P < 0.05$). However, there were no significant differences in blood pressure, pulse rate and circulating plasma volume between both groups.

iii) Peripheral blood serotonin (Fig. 26)

In four out of five cases, peripheral blood serotonin levels in the cases of preservation increased markedly 10 minutes after glucose ingestion, while the increase was slight in the

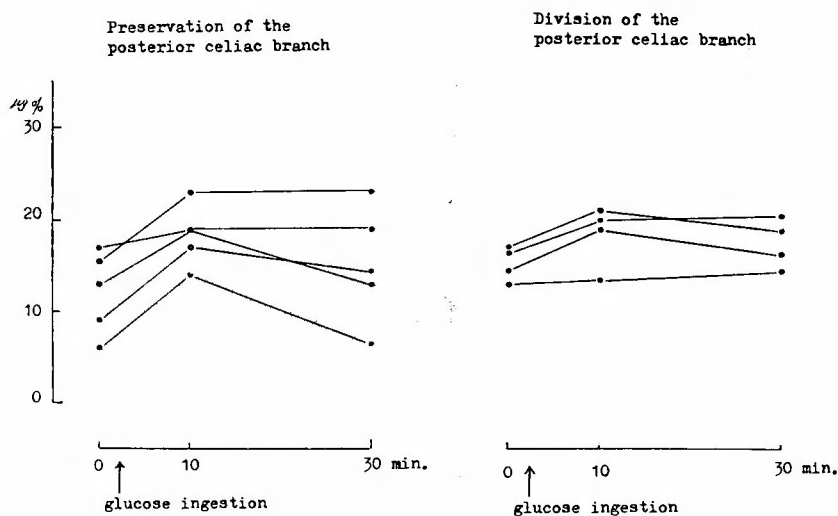


Fig. 26 Increase in peripheral blood serotonin levels following glucose ingestion after total gastrectomy

cases of total vagotomy.

II. Dumping provocation test in the colon

i) Subjective symptoms

Following administration of 150 milliliter of 50 per cent glucose solution through the artificial anus into the colon, the dumping symptoms were not observed.

ii) Systemic hemodynamics (Fig. 27)

During the dumping stimulus, the colon showed 4.2 ± 2.53 per cent rise of maximal blood pressure, 4.9 ± 2.66 per cent increase of pulse rate, 3.0 ± 1.30 per cent decrease of circulating plasma volume and $0.5 \pm 0.17^\circ\text{C}$. elevation of skin temperature, while the jejunum showed 14.3 ± 1.54 per cent, 31.9 ± 3.37 per cent, 13.4 ± 3.03 per cent and $2.9 \pm 0.43^\circ\text{C}$. elevation, respectively.

There were significant difference in blood pressure, pulse rate, circulating plasma volume and skin temperature between both groups.

iii) Peripheral blood serotonin (Fig. 28)

Peripheral blood serotonin levels in four out of five cases of the jejunum increased markedly 10 minutes after glucose ingestion, while the increases in the cases of the colon were slight.

III. The dumping test in the patients with intestinal transposition

The dumping test following ingestion of 150 milliliter of 50 per cent glucose solution was performed in a patient with jejunal transposition and in a patient with ileo-colonic transposition. The patient with jejunal transposition complained of flushing and abdominal fullness, in contrast to no complaints from the patient with ileo-colonic transposition.

The patient with jejunal transposition showed 10.4 per cent elevation of blood pressure, 41.9 per cent elevation of pulse rate and 4.9°C . elevation of skin temperature, while the patient with ileo-colonic transposition showed 15.3 per cent, 25.0 per cent and 0.1°C .

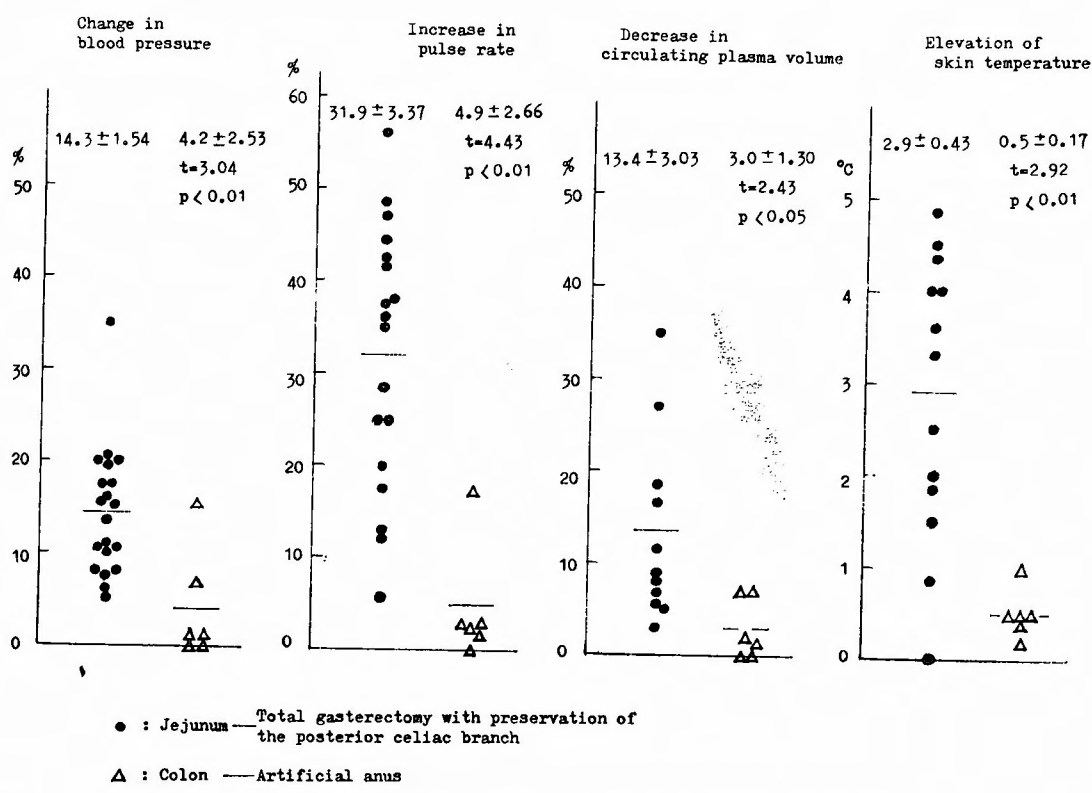


Fig. 27 Changes in systemic hemodynamics in postoperative dumping test

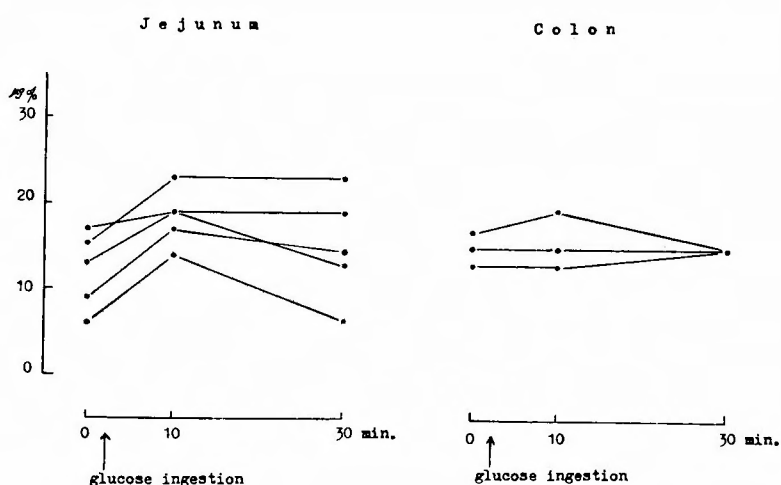


Fig. 28 Increase in peripheral blood serotonin levels in postoperative dumping test

elevation, respectively. In each patient peripheral blood serotonin levels increased 0.07 microgram per milliliter and 0.04 microgram per milliliter, respectively, 10 minutes after glucose ingestion. However, the per cent increase in the patient with jejunal transposition was 116 per cent, markedly higher than 36 per cent in the patient with ileo-colonic transposition.

Discussion

1. Systemic hemodynamics and serotonin in dumping

It has been generally accepted that main factors in the pathogenesis of the dumping syndrome are the disturbance of the microcirculation in the portal area with the resulting decrease in circulating blood volume⁴⁾¹⁶⁾³⁶⁾⁵⁰⁾⁵⁴⁾⁶⁹⁾⁷⁴⁾, and the release of serotonin and other humoral agents secondary to rapid transit of a hyperosmolar meal into the upper small intestine. However, the quantitation of the intensity of the dumping syndrome is difficult, because this syndrome is essentially based on subjective symptoms.

It is well known that the dumping syndrome is accompanied with decreased circulation blood volume, increased pulse rate, changes in blood pressure (mostly hypotension), elevated skin temperature and increased peripheral blood volume, which are closely related to the dumping symptoms such as palpitation, vertigo and flushing⁴⁶⁾⁷⁰⁾. In addition, several investigations have shown that these cardiovascular symptoms and signs may be caused by the release of humoral agents and the disturbance of the microcirculation in the portal area.

O'HARA⁴⁵⁾ and other investigators¹⁾¹⁰⁾²⁸⁾²⁹⁾³⁸⁾⁴²⁾⁶⁸⁾ have shown the close relationship of serotonin to the dumping syndrome. Probably the rapid release of serotonin from the enterochromaffin cells may be the initiating factor of the dumping syndrome. The released serotonin causes nausea, flushing, diarrhea and a decrease in peripheral blood flow detected by digital plethysmography⁶³⁾⁷⁰⁾.

Moreover, the local effect of serotonin causes the disturbance of the microcirculation, such as increase in permeability of the capillary and pooling of blood in the portal area¹³⁾.

From the above evidence it may be said that changes in systemic hemodynamic and serotonin are closely related to the dumping syndrome, and reliable indicators for the intensity of this syndrome.

2. Intestinal variety of substitute stomach and dumping

The segments of upper small intestine, colon and ileo-colon have been used as substitute stomach after total gastrectomy. In the present experimental and clinical studies, the colon showed a lesser alteration in systemic hemodynamics and portal serotonin levels in response to the dumping stimulus.

It is speculated that three factors may participate in the lesser alteration in portal serotonin levels in the colon. The first factor is that serotonin content in the colon is smaller than that in the small intestine. This finding was seen in men by RESNICK & GRAY⁵³⁾ and in dogs by ERSPAMER¹²⁾. The present study by fluorohistochemistry obtained the same results in dogs; serotonin content in the colon was only a half of that of the small intestine. And the decrease of intestinal serotonin content in response to the dumping stimulus was slight in the colon.

The second factor is intraluminal pressure. It has been accepted that the release of serotonin is affected by intraluminal pressure. SILVER et al⁵⁸⁾ observed that jejunal serotonin was released above 15 millimeter Hg of intraluminal pressure. In the present study, however, intraluminal pressure can not be considered a factor responsible for the difference in portal serotonin levels, because there was no difference in intraluminal pressure between the small intestine and colon during the dumping test. The third factor is the length of the intestine which contacts with hypertonic glucose solution. That is much shorter in the

colon as compared with the jejunum.

Therefore, the increase in portal serotonin levels in response to the dumping stimulus would be slight in the colon, even though the amount of serotonin released from the same length of the small intestine and colon were the same. The observation that a less marked difference in the rise of portal serotonin levels was noted between the jejunum and colon in the present experiment of interposition using the same length of the intestinal segment seems to be explained, at least in part, by this factor. On the other hand, changes in systemic hemodynamics in response to the dumping stimulus were exceedingly slight in the colon.

These observations indicate that the dumping responses in the colon are remarkably slight as compared with the small intestine, although this is less marked in the interposed colonic segment.

3. Vagal innervation and dumping

The clinical observations have shown that the dumping syndrome occurs more frequently in the patients with vagotomy²⁾⁹⁾³¹⁾, and in the patients with selective vagotomy than in the patients with truncal vagotomy¹⁹⁾²²⁾³³⁾⁶⁶⁾, and vagolytic agents are effective for the dumping syndrome in the therapeutic means⁸⁾⁹⁾³⁵⁾⁷²⁾. These observations suggest a close relationship of the vagal innervation to the pathogenesis of the dumping syndrome. In addition, LIN³⁴⁾ observed in dogs that an increase in portal venous PO₂ and pressure in the experimental dumping was suppressed by truncal vagotomy. In respect to changes of humoral agents in the experimental dumping, UENO et al⁶⁷⁾ showed that celiac vagotomy suppressed a rapid rise in portal serotonin levels, while WATANABE et al⁷¹⁾ observed that total or posterior celiac vagotomy produced a marked increase in serotonin with a decrease in histamin of the portal vein.

WAKABAYASHI⁶⁸⁾, in our laboratory, showed that posterior celiac vagotomy suppressed an alteration of systemic hemodynamics and the disappearance of serotonin fluorescence in the jejunal mucosa following the administration of hypertonic glucose solution into the upper jejunum. Moreover, the present study showed that a rapid rise in portal serotonin levels in response to the dumping stimulus was suppressed by posterior celiac vagotomy. In fluorohistochemical study, no appreciable increase in serotonin content was detected in the dog jejunum two weeks after posterior celiac vagotomy, although TOBE et al⁶⁵⁾ observed an increase in serotonin content in the rat stomach two to three weeks after total vagotomy. Therefore, the slower rise in portal serotonin levels shows that the release of serotonin from the jejunal mucosa into the portal vein is suppressed by posterior celiac vagotomy.

In the colon, on the other hand, changes in systemic hemodynamics and portal serotonin levels in response to the dumping stimulus were slight and the effects of posterior celiac vagotomy on the dumping responses were minimal or none. This can be explained by the facts that vagal innervation of the colon is weak and is limited to the proximal half of the colon.

The role of the posterior celiac vagus in the release of serotonin is not established. It is well known that the increased peristaltic activity and intraluminal pressure cause the release of serotonin from the intestine⁶⁾³⁰⁾. Because the vagal nerve transmits mechanical and chemical stimuli added to sensory receptors in the intestinal mucosa, it is quite possible that intrajejunal administration of hypertonic glucose solution causes an increase in

peristaltic activity and intraluminal pressure by the vagal reflex and results in the release of serotonin from the intestine. In addition, there is some evidence that efferent vagal impulse causes the release of serotonin. BÜLBRING et al.⁷⁾ and STRAUSS et al.⁶¹⁾ showed that electrical stimulation of the vagus accelerates the release of serotonin from the stomach or small intestine. TOBE et al.⁶⁵⁾ emphasized the vagal release of serotonin from the observations that total vagotomy produced an increase in serotonin content of the stomach, while electrical stimulation of the vagus produced a decrease in serotonin content of the stomach with an increase in portal serotonin levels.

It is speculated that three factors may pertain to the role of the vagus in the alteration of systemic hemodynamics in the dumping syndrome: the so-called vagal reflex, the release of humoral agents and the disturbance of the microcirculation in the portal area.

Because the risen blood pressure with the decreased pulse rate described as the signs of the vagal reflex³⁷⁾ does not correspond to the cardiovascular signs of the dumping syndrome, the vagal reflex is not considered to play a role in the alteration of systemic hemodynamics in this syndrome. Vagal release of humoral agents other than serotonin is not established. However, histamine and catecholamine, which are closely related to cold sweating, palpitation, flushing, increased peripheral blood flow and decreased circulating blood volume in the dumping syndrome, may be caused by vagally released serotonin¹³⁾³⁹⁾⁴⁰⁾.

As compared with the patients of total gastrectomy with truncal vagotomy, the patients of total gastrectomy with preservation of the posterior celiac vagus showed a higher incidence of dumping symptoms, especially Group A symptoms, such as cold sweating and palpitation, and a more marked elevation in skin temperature in the dumping provocation test. The elevated skin temperature is due to the increased peripheral blood flow²⁰⁾²¹⁾, which is closely related to histamine and bradykinin⁶²⁾⁷⁰⁾. These clinical observations suggest that some cardiovascular symptoms may be caused by humoral agents released by the posterior celiac vagi.

There are but few data concerning the effect of the vagus on the disturbance of the microcirculation in the portal area. PELLEGRINI⁴⁸⁾ observed in the rat peritoneum that vagotomy produced constriction of small vessels, while vagal stimulation caused dilatation of small vessels, especially the venules, and the stoppage of blood flow in the capillaries. LIN³⁴⁾ observed in dogs that truncal vagotomy suppressed an increase in PO_2 and pressure of the portal vein in the experimental dumping, suggesting the alleviating effect of vagotomy on the disturbance of the microcirculation in the portal area. Presumably, in the experimental dumping, the posterior celiac vagi accelerates the release of humoral agents including serotonin and aggravates the disturbance of the microcirculation in the portal area by vagal vasomotor reflex and local effects of vagally released humoral agents. And posterior celiac vagotomy may result in the reduction of the dumping responses by blocking these mechanisms.

On the other hand, the role of the hepatic vagi in the dumping syndrome remains unknown. Because hepatic vagotomy may affect hepatic functions³⁾¹⁸⁾⁵⁵⁾ and the liver is a main organ metabolizing serotonin¹¹⁾⁴¹⁾⁶¹⁾, it is possible that the hepatic vagi may play a role in the dumping syndrome through serotonin metabolism.

However, the present study showed no significant difference in serotonin clearance by the liver between the experimental groups with and without hepatic vagotomy. Therefore,

it is considered that the hepatic vagi has no relation to the dumping syndrome from the standpoint of serotonin metabolism.

4. Type of reconstruction by means of substitute stomach and dumping

Esophagojejunostomy and interposition with jejunal segment between the esophagus and duodenum have been widely used as reconstruction modes after total gastrectomy. Because rapid transit of a hyperosmolar meal into the upper small intestine is a trigger to induce the dumping syndrome, this syndrome can be prevented by the improvement of reconstruction modes after total gastrectomy. MURAKAMI⁴⁹⁾ observed that the dumping syndrome in the patients without jejunal interposition occurred in as high as 33 per cent and was severe, while the syndrome in the patients with jejunal interposition occurred in 20 per cent and was slight. KONDO³²⁾ reported that the dumping syndrome was rare in the patients with transposition of figure 6-shaped jejunal loop.

The present study showed that decrease in pulse pressure in the experimental groups of double tract and transposition of figure 6-shaped loop was significantly slight as compared with in the experimental group of simple interposition, although no appreciable difference was found in serotonin levels of portal and systemic venous blood. These observations support the view that reconstruction modes by means of substitute stomach, such as double tract or transposition of figure 6-shaped loop, prevent, to some degree, the dumping syndrome.

5. Considerations of substitute stomach regarding prevention of the dumping syndrome

The present study on substitute stomach after total gastrectomy indicates that preservation of the posterior celiac vagus has the strongest influence on the dumping responses and the role of the different kinds of interposed intestinal segments in the dumping responses is more important than that of reconstruction modes, judging from the alteration of blood serotonin levels and systemic hemodynamics. It is well known that the dumping syndrome is relatively rare in the patients with total gastrectomy or the radical operation for gastric cancer⁵⁾, although the incidence of this syndrome is high in the patients with higher gastric resections⁴⁷⁾⁷³⁾.

These findings suggest that truncal vagotomy may result in a lower incidence of the dumping syndrome, because truncal vagotomy is usually performed in total gastrectomy or the radical operation for gastric cancer. It is generally accepted that the interposition of jejunal segment between the esophagus and duodenum is a satisfactory reconstruction mode by means of substitute stomach in the activity of gastric reservoir, the prevention of reflux esophagitis and the dumping syndrome, and the improvement of digestive and absorptive functions of the intestine.

The previous studies¹⁴⁾¹⁵⁾²⁴⁾²⁵⁾²⁶⁾⁶⁸⁾ in our laboratory showed that preservation of the posterior celiac vagus prevented the occurrence of postoperative complaints, such as diarrhea, weightloss and anorexia, and improved the disturbance of fat absorption and glucose metabolism following total gastrectomy. Therefore, the interposition of intestinal segment with preservation of the vagus is considered to be the best reconstruction mode by means of substitute stomach from the standpoint of postoperative nutritional disturbances. The only disadvantage of this reconstruction mode is the more frequent occurrence of the dumping syndrome. In order to cope with this disadvantage it seems reasonable that the colonic

segment rather than the jejunal segment be used as substitute stomach and the transposition of figure 6-shaped loop or double tract anastomosis be performed in the case of the small intestine. Especially, the interposition of ileo-colon segment with Bauhin's valve is considered to be excellent in the prevention of the occurrence of the dumping syndrome.

Summary

The relationship of the qualities of substitute stomach, after total gastrectomy, to the dumping syndrome was studied experimentally and clinically.

The intensity of the dumping responses following hypertonic glucose administration was judged from changes in systemic hemodynamics and blood serotonin levels. The results obtained were as follows :

(1) In dogs, the alteration of the systemic hemodynamics and the rise of blood serotonin levels following intra-intestinal glucose administration were significantly marked in the jejunum as compared with the colon, serotonin content of which was about a half of that of the jejunum.

(2) In the dumping test in the experimental model of intestinal transposition, there was a significant difference in the decrease of pulse pressure between the jejunum and the colon, although no significant differences were observed in regard to femoral artery pressure and blood serotonin levels.

(3) The intensity of the dumping responses in the dog jejunum was markedly slight in the group with posterior celiac vagotomy as compared with the group without the vagotomy. However, the effect of posterior celiac vagotomy on the dumping responses following intracolonic glucose administration were minimal or none.

(4) In the group of the transposed jejunal segment with posterior celiac vagotomy, the decrease in pulse pressure was slight and the initial rise in portal serotonin levels was less marked, as compared with the group without the vagotomy. These effects of posterior celiac vagotomy were also observed in the group of transposed colonic segment.

(5) No significant difference in the dumping responses was observed between the groups with and without hepatic vagotomy.

(6) In the group of the jejunal transposition without posterior celiac vagotomy, the decrease in femoral artery pressure and the increase in blood serotonin levels showed little difference among the groups of simple transposition, figure 6-shaped loop transposition and double tract anastomosis. However, the decrease in pulse pressure in the latter two groups was slight than the former group, with a significant difference between the group of simple transposition and double tract anastomosis.

(7) In the patients of total gastrectomy with posterior celiac vagotomy, the incidence of the systemic dumping symptoms, especially Group A symptoms, was slight and the elevation of digital skin temperature in the dumping test was less marked, as compared with the patients of total gastrectomy without the vagotomy.

Moreover, systemic vein serotonin levels showed a more marked increase in the patients without the vagotomy.

(8) In the dumping test following hypertonic glucose administration through the artificial anus into the colon, the dumping symptoms were not observed and the dumping responses

were very slight.

From these observations it may be concluded that, in the dumping syndrome after total gastrectomy, innervation of the posterior celiac vagus in substitute stomach plays a major role and the role of intestinal variety of substitute stomach is more important than that of reconstruction modes.

From the standpoint of the prevention of the dumping syndrome in total gastrectomy with preservation of the posterior celiac vagus, it may be said that the colonic transposition is better than the jejunal transposition and the transposition of figure 6-shaped loop or double tract anastomosis is recommended in the case of the jejunum.

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和文抄録

胃全摘術後の代用胃とダンピング症候群に関する研究

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胃全摘術後障害に対する対策として、迷走神経肝枝および後腹腔枝を保存する迷走神経部分的保存胃全摘術(木村・石上)を施行すると、従来の全迷走神経切断を伴う胃全摘例に比べて、下痢、食思不振、体重減少などの自觉症状、脂肪吸収能、耐糖能、胆嚢機能などは著しく改善されるにもかかわらずタンピング症候群だけは頻発する傾向がある。ダンピング症候群の発生は患者の食物摂取を著しく制限し、とくに胃全摘術後には栄養吸収の面からの障害が必発するので、ダンピング症候群の発生を防止することは、術後栄養障害の点から重要な意味をもっている。ダンピング症候群の発生機序については、最近とくにセロトニンを初めとする体液性因子と全身および門脈系の循環動態の面から検討が加えられているが、ダンピング症候群の発生防止対策としては、このような発生機序にもとづいた検討が必要である。

今回の研究では、胃全摘術後のダンピング症候群の発生に関して、高張糖液負荷試験におけるセロトニンと全身循環動態の変化を示標として、代用胃の面から(1)腸管の種類、(2)迷走神経支配、(3)再建様式について、臨床的観察ならびにイヌにおける実験の結果から検討を加え、次のような成績を得た。

1) イヌにおける高張糖液負荷試験では、結腸は空腸に比較して、全身循環動態および血中セロトニンからみたダンピング反応は非常に軽度で、結腸粘膜上皮に含まれるセロトニン量も空腸の約1/2であった。

2) イヌの有茎移植腸管における高張糖液負荷試験では、脈圧については空腸移植群と結腸移植群との間に有意差を認めた。しかし股動脈圧および血中セロトニンについては、ほとんど差を認めなかった。

3) イヌにおいて迷走神経後腹腔枝を切断した場合、空腸ではダンピング反応が非常に軽度になったが、結腸は後腹腔枝切断の影響をほとんど受けなかつ

た。

4) イヌの有茎移植空腸において、後腹腔枝を切断した場合には、脈圧の減少と門脈血中のセロトニンの早期上昇が軽度となった。この後腹腔枝切断の影響は移植結腸においてもみられた。

5) 迷走神経肝枝切断はダンピング反応にほとんど影響を与えなかった。

6) 後腹腔枝保存群において、単純移植、6字型移植および重複腸管の移植空腸では、股動脈圧および血中セロトニンについては、この3群に著しい相違を示さなかったが、脈圧減少率は後2群において軽度の傾向を示し、とくに単純移植と重複腸管の間に有意差を認めた。

7) 臨床的に迷走神経部分的保存胃全摘例は後腹腔枝切断例に比べてダンピングの全身症状、とくにA症状の発現頻度が高く、高張糖液負荷試験で指尖皮膚温の上昇がつよく、末梢血中セロトニンの早期上昇がみられた。

8) 臨床的に結腸における高張糖液負荷試験ではダンピング症状の発現は全くなく、またダンピング反応は非常に軽度にとどまった。

以上の成績から、胃全摘術後のダンピング症候群の発現には、迷走神経後腹腔枝支配がもっとも大きな役割を演じ、次いで吻合形式よりも胃全摘後に使用される代用胃の性状が関与すると考えられる。したがって迷走神経部分的保存胃全摘術後におけるダンピング症候群の発生防止の点からみれば、代用胃として空腸を用いる場合には、再建様式としては、単純移植より6字型腸管移植または重複腸管の方がすぐれていると思われる。また、結腸は空腸よりダンピング症候群の発生防止の点ではすぐれており、とくにBauhin弁を利用できるileo-colonの移植は効果的で、術後障害防止の点ではもっともすぐれていると考えられる。